FDA is incapable of protecting US "against another Vioxx"

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The approval of rofecoxib (Vioxx) by the US Food and Drug Administration has led to the "single greatest drug safety catastrophe in the history of this country or the history of the world," charged one of the agency's own experts, Dr David Graham, in US Senate hearings last Thursday.

Dr Graham, associate director in the FDA's Office of Drug Safety, said an estimated 88 000 to 139 000 Americans had heart attacks and strokes as a result of taking rofecoxib. The number, he said, far exceeds earlier disasters such as the 100 children killed in the United States by an elixir of sulfanilamide in the 1930s and the 5000 to 10 000 children born in the 1960s with birth defects related to thalidomide. Both events led to sweeping regulatory changes in the United States.

Senator Charles Grassley, chairman of the Senate's finance committee, opened the hearings on the FDA and rofecoxib and its manufacturer, Merck, saying he hoped Congressional investigation would help shed "disinfecting sunlight" on the approval of rofecoxib by the FDA and its subsequent withdrawal by Merck on 30 September, when the company acknowledged that the drug carried "serious cardiovascular risks" (*BMJ* 2004;329:816, 9 Oct).

Senator Grassley charged that the FDA "has lost its way when it comes to making sure drugs are safe" and that its relationship with drug companies was "too cosy."

Dr Graham agreed, saying sweeping changes were needed again because the FDA "as currently configured is incapable of protecting America against another Vioxx." In response to questioning, Dr Graham indicated that five other drugs currently on the market may be endangering patients, including another cyclo-oxygenase-2 inhibitor, valdecoxib (Bextra; made by Pfizer), the weight loss drug sibutramine (sold as Reductil in Britain and Meridia in the United States), the lipid lowering drug rosuvastatin (Crestor; made by AstraZeneca), the acne drug isotretinoin (Roaccutane; Roche), and the asthma drug salmeterol (Serevent; A&H).

Dr Graham suggested that Congress look to Europe, where some regulatory processes better protect the public. One such change would be to grant the Office of Drug Safety independent regulatory authority. Currently safety officers have to "convince" the Office of New Drugs that a drug has a problem, said Dr Graham. That creates an "inherent conflict of interest," because the "same group that approved the drug is also responsible for taking regulatory action against it post-marketing."

Dr Sandra Kweder, deputy director of the Office of New Drugs, dismissed Dr Graham's charges that the FDA failed to protect the public, saying that Merck's decision to voluntarily withdraw rofecoxib was the result of the "FDA's vigilance in requiring long term outcome trials to address our concerns."

Other FDA officials were outraged by Dr Graham's testimony. Dr Steven Galson, director of the agency's Center for Drug Evaluation and Research, was quoted in the *New York Times* (www.nytimes.com) on 20 November as saying that Dr Graham's assertions were "irresponsible."

The FDA issued a statement after the hearings claiming that Dr Graham had failed to adhere to agency protocol when he submitted data to the *Lancet* from a study he led in cooperation with the healthcare organisation Kaiser Permanente of northern California. The study, which looked at cardiovascular risks in patients taking rofecoxib, was to have been published last week in the *Lancet* but was pulled at the last minute after Dr Graham had a warning from his supervisor about the publication.

AP PHOTO/GERALD HERBERT

Dr David Graham suggested that the public would be better protected if the FDA's Office of Drug Safety were granted independent regulatory authority

Merck also came under fire for promoting rofecoxib even after its scientists were aware of potential serious cardiovascular risks. Dr Gurkipal Singh, adjunct clinical professor of medicine at Stanford University, testified that as early as November 1996 Merck scientists "were seriously discussing a potential [heart attack] risk of Vioxx."

Dr Singh reviewed email messages submitted to Congress that documented conversations among Merck scientists in 1997 about whether to include patients taking aspirin in clinical trials, as aspirin might negate the gastrointestinal benefits of rofecoxib. This caused one Merck scientist to comment that if aspirin use was forbidden, patients on rofecoxib might have more heart attacks and that would "kill the drug," but he also pointed out that "everyone is on it [aspirin]."

Merck's failure to undertake a study of cardiovascular outcomes was a "marketing decision" designed to minimise the possibility of finding cardiovascular adverse events, said Dr Singh. He added: "It would be better to kill the drug than to kill the patient."

Merck's president, Raymond Gilmartin, defended his company's actions, saying that it believed that the benefits of fewer gastrointestinal events outweighed the cardiovascular risks. His confidence in rofecoxib was so great, Mr Gilmartin said, that his wife "was a user of Vioxx until the day we withdrew it from the marketplace."

Four of the five companies whose drugs Dr Graham said might be endangering patients, have defended their drugs' safety when used as indicated. One company, Roche, had no comment to make on the allegations. (See p 1255.) □